

PROSTATE SPECIFIC ANTIGEN AND TYPE 2 DIABETES: A PRELIMINARY REPORT

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SUMMARY

The aim of the present study was to assess and compare the values of prostate specific antigen (PSA) in serum of diabetic subjects and non-diabetic controls in search for possible relationships. The study included 59 diabetic men aged 28-71 (56±9) years and 63 non-diabetic men aged 33-63 (49±7) years. PSA was measured with two-site fluoroimmunoassay. The values of PSA in the two groups subdivided according to age (<50 and ≥50 years) were compared by Mann-Whitney U test and linear correlation. There was a correlation between PSA and age in the group of men free from diabetes ($r=0.428$; $p=0.0005$), however, it was lower in diabetic subjects ($r=0.309$; $p=0.017$). Study results indicated the values of PSA to be more age dependent in non-diabetic than in diabetic subjects.

INTRODUCTION

Prostate specific antigen (PSA) is a glycoprotein produced primarily by the epithelial cells of the prostate gland, and its regulation is under the control of androgens and progestins. It is a serine protease with chymotrypsin-like enzymatic activity and has a molecular weight of about 30 kDa. PSA is secreted into seminal plasma at a high concentration (~0.5-3 g/L), whereas lower (~10⁶ times) concentrations normally found in the circulation are the result of leakage from

the prostate gland (1,2). PSA at lower concentrations has recently been also detected in many tissues, especially female breast (3).

The PSA gene is member of the human kallikrein gene family, which consists of at least 14 genes. All of them, which encode for serine proteases, have significant homologies and structural similarities (3). Three major PSA fractions, the complex of PSA and α 2-macroglobulin, the complex of PSA and α 1-antichymotrypsin (PSA-ACT) and free, uncomplexed PSA, have been identified in serum. Immunoaccessible (total) PSA in serum is mostly found as a PSA-ACT complex and free PSA (representing about 10%-30% of total PSA) (4,5).

The physiological function of PSA is not yet entirely understood; it is possible that it is related to the activity of kallikreins. The well-known and accepted physiological function is that PSA proteolytic cleaves seminogelins and fibronectin are present in seminal plasma and thus cause liquefaction of the seminal clot after ejaculation. This process does promote the release and motility of sperm cells (6,7). Other potential functions, i.e. activity of PSA, imply its role as a cell growth inhibitor, an anticarcinogenic/antiangiogenic molecule, or inducer of apoptosis (3).

PSA is the most valuable prostatic cancer marker that is used for population screening, diagnosis, and monitoring of patients with prostate cancer (1). There are some epidemiologic studies on the relationship

among diabetes, prostate cancer risk, and PSA, however, the results have often been discrepant and confusing.

Diabetes mellitus is a growing health problem due to the chronic nature of the syndrome and increasing prevalence, especially in developing world (8,9). Current classification of diabetes mellitus, proposed by the American Diabetic Association (ADA) in 1997 (10,11) and accepted in a slightly revised form by the World Health Organization (WHO) (12), divides it into four main types: type 1 diabetes is less common (less than 10% of the total number of diabetics have this type of disease) and its basic characteristic is the lack of insulin caused by predominantly autoimmune destruction of pancreatic β cells; type 2 diabetes, which is much more common, has two different defects, i.e. insulin resistance and failure of β cells to secrete insulin adequately (13). Not all patients reach the stage of insulin requirement for treatment. However, in some type 2 patients insulin deficiency may become so profound that they need insulin permanently. In principle, the longer the duration of diabetes, the more prominent the β cell failure; other specific types of diabetes and gestational diabetes are the remaining two classes.

In this study, we compared the values of PSA in serum of diabetic subjects and subjects free from diabetes, in search for potential relationships.

PATIENTS AND METHODS

Fifty-nine men with type 2 diabetes aged 28-71 (56 ± 9) years and 63 non-diabetic men aged 33-63 (49 ± 7) years as controls, referred to the clinic for medical general check-up by their employers, were included in the study. For these reasons, the ideal age matching could not be obtained. In addition to other laboratory parameters, PSA was measured in serum by fluoroimmunometric assay using commercially available DELFIA reagent kit (Wallac Oy, Turku, Finland). The assay is a solid phase, two-site immunofluorometric assay based on the direct sandwich technique using two monoclonal antibodies (derived from mice). The measuring range of the assay is up to 500 $\mu\text{g/L}$, and the reference limit is 0-4.0 $\mu\text{g/L}$. The intra- and inter-assay variation is 4.6% and 5.6%, respectively.

Mann-Whitney U test and linear correlation were used to compare the values of PSA between the two main groups (diabetic and non-diabetic subjects) and age subgroups (<50 and ≥ 50 years of age).

RESULTS

All PSA values for both groups were within the normal range, two of them being at the upper limit. Descriptive data for non-diabetic and diabetic subjects aged <50 and ≥ 50 years are presented in Table 1. Mann-Whitney U test yielded no statistically significant differences in PSA values between the main groups and subgroups. Some tendency of difference was only observed between the <50 and ≥ 50 non-diabetic subgroups, with a higher PSA value in the latter ($p=0.056$).

Table 1. Descriptive statistics data of PSA

Group	n	Mean ($\mu\text{g/L}$)	SD	M ($\mu\text{g/L}$)	Min ($\mu\text{g/L}$)	Max ($\mu\text{g/L}$)	
Diabetic	<50 yrs	15	0.56	0.16	0.60	0.32	0.87
	≥ 50 yrs	44	0.92	0.70	0.71	0.16	3.60
Non-diabetic	<50 yrs	34	0.65	0.33	0.60	0.20	1.70
	≥ 50 yrs	29	1.25	1.12	0.70	0.20	4.90

Accordingly, in the group of non-diabetics, a correlation between PSA and age was confirmed ($\text{PSA} = -1.365 + 0.0475 \cdot \text{Age}$ with correlation $r=0.428$; $p=0.0005$) (Fig. 1). In diabetic subjects, this correlation was lower ($\text{PSA} = -0.313 + 0.020 \cdot \text{Age}$ with correlation $r=0.309$; $p=0.017$) (Fig. 2). Considering the figures together, it is seen that at 40 years of age the PSA value was 0.5 $\mu\text{g/L}$ in both groups, whereas at the age of 65 it was 1.75 and 1.0 $\mu\text{g/L}$ in the non-diabetic and diabetic group, respectively.

Figure 1. Linear correlation PSA vs. age in non-diabetic group

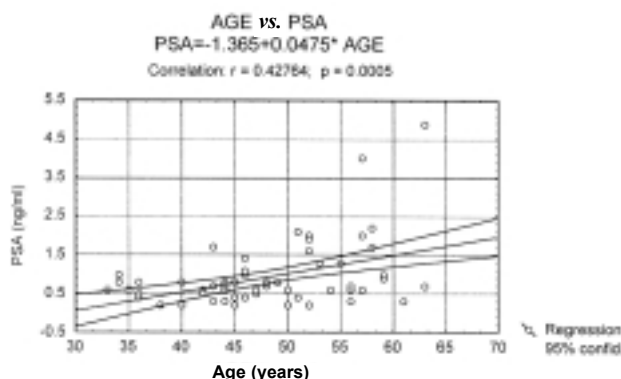
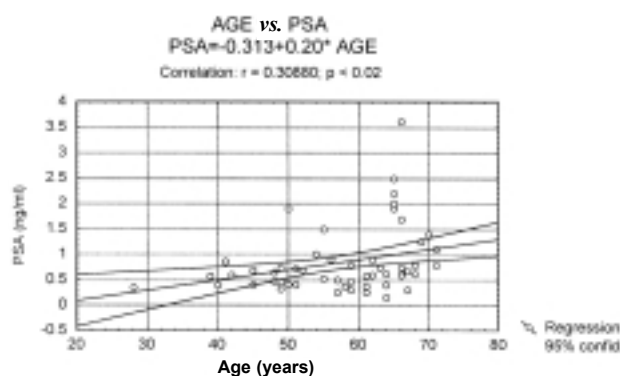


Figure 2. **Linear correlation PSA vs. age in diabetic group**



DISCUSSION

PSA is the most useful biomarker for the detection and monitoring of prostate cancer. Elevated serum PSA concentrations are known to be connected with the three most common prostatic diseases, i.e. prostate cancer, benign prostatic hyperplasia, and prostatitis (1-3). A variety of factors can affect PSA and should be taken in consideration on interpretation of results. Physical activity, infection, and medicaments can cause secondary elevations of PSA; also, prostate biopsy and cystoscopy usually cause substantial PSA elevation. And finally, some medications can suppress PSA causing false-negative results (2).

Serum PSA concentration is age dependent, i.e. it tends to increase with age because the prostate enlarges with years and contains more PSA-producing tissue (14). Results from epidemiologic studies on the relationship between diabetes and prostate cancer risk are often confusing. Some studies suggest a lower risk of prostate cancer among diabetics. This relationship was investigated in the Health Professionals Follow-Up Study conducted from 1986 till 1994 in the United States. The basis of this relationship is unclear, however, it may reflect hormonal changes associated with diabetes, maybe low testosterone level (15). Other epidemiologic studies have provided little support to the hypothesis that prostate cancer risk is increased in men with elevated total or bioavailable

testosterone (16). Results of the Cancer Prevention Study (1959-1972) have indicated that men who had diabetes mellitus for five or more years had a higher incidence of prostate cancer than men without diabetes (17). Another case-control study also found an association between diabetes and prostate cancer (18). Results of a population-based study of Chinese men suggest that higher serum insulin levels may influence the risk of prostate cancer in Chinese men (19).

In contrast to these, case-control studies in north Italy found no relationship between diabetes and risk of prostate cancer (an increased risk of cancer of the liver, pancreas and endometrium was observed) (20).

Results of our study indicated that in diabetic subjects, the values of PSA were less age dependent than in non-diabetic subjects, particularly among the elderly. The observed tendency of elderly diabetics to have lower serum PSA levels may be ascribed to the diminished capacity of the prostate to produce PSA or to its decreased leak due to the preserved cell integrity. It is widely accepted that in a patient with prostate cancer, elevation of the serum PSA concentration is attributable to the increased cell count, destruction of prostatic architecture, and higher PSA levels in the circulation (3).

Considering suggestions from other studies about the lower risk of prostate cancer among diabetics (15), the data obtained in our study would not support the concept according to which the lower PSA levels in our diabetic subjects older than 65 might express a lower risk of prostate cancer, however, this hypothesis should not be definitely abandoned. Other urologic examinations that were beyond the main purpose of the study and larger groups of subjects should be included to obtain more information on the issue.

On the other hand, if the tendency to lower serum PSA levels in elderly diabetics is the consequence of the decreased prostatic cell capacity to produce PSA, it could also increase the risk of prostate cancer, taking into account the tumor suppressive activities of PSA (3). It appears that our preliminary results have left all issues unresolved.

REFERENCES

1. Diamandis EP. Prostate-specific antigen: its usefulness in clinical medicine. *Trends Endocrinol Metab* 1998;9:310-316.
2. American Urological Association. Prostate-specific antigen (PSA) best practice policy. *Oncology* 2000;14:267-286.
3. Diamandis EP. Prostate-specific antigen: a cancer fighter and a valuable messenger? *Clin Chem* 2000;46:896-900.
4. Lilja H, Christensson A, Dahlen U, et al. Prostate-specific antigen in serum occurs predominantly in complex with alpha 1-antichymotrypsin. *Clin Chem* 1991;37:1618-1625.
5. Stenman UH, Leinonen J, Alfthan H, et al. A complex between prostate-specific antigen and alpha 1-antichymotrypsin is the major form of prostate-specific antigen in serum of patients with prostatic cancer: assay of the complex improves clinical sensitivity of cancer. *Cancer Res* 1991;51:222-226.
6. Lilja H. Seminal vesicle-secreted proteins and their reactions during gelation and liquefaction of human semen. *J Clin Invest* 1987;80:281-285.
7. Christensson A, Laurell CB, Lilja H. Enzymatic activity of prostate-specific antigen and its reactions with extracellular serine proteinase inhibitors. *Eur J Biochem* 1990;194:755-763.
8. Hanley AJG, McKeown-Eyssen G, Harris SB, et al. Cross-sectional and prospective associations between proinsulin and cardiovascular disease risk factors in a population experiencing rapid cultural transition. *Diabetes Care* 2001;24:1240.
9. Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. *JAMA* 2001;286:1195.
10. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 1997;20:1183.
11. Kuzuya T, Matsuda A. Classification of diabetes on the basis of etiologies versus degree of insulin deficiency. *Diabetes Care* 1997;20:219.
12. World Health Organization. Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO Consultation, Part 1: Diagnosis and classification of diabetes mellitus. Geneva: WHO/NCD/NCS/99.2, 1999.
13. Weyer C, Tataranni PA, Bogardus C, Pratley RE. Insulin resistance and insulin secretory dysfunction are independent predictors of worsening of glucose tolerance during each stage of a diabetes development. *Diabetes Care* 2001;24:89.
14. Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men: establishment of age-specific reference ranges. *JAMA* 1993;270:860-864.
15. Giovannuci E, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Diabetes mellitus and risk of prostate cancer (United States). *Cancer Causes Control* 1998;9:3-9.
16. Kaaks R, Lukanova A, Sommersberg B. Plasma androgens, IGF-1, body size and prostate cancer risk: a synthetic review. *Prostate Cancer Prostatic Dis* 2000;3:157-172.
17. Will JC, Vinicor F, Calle EE. Is diabetes mellitus associated with prostate cancer incidence and survival? *Epidemiology* 1999;10:313-318.
18. Ilic M, Vlajinac H, Marinkovic J. Case-control study of risk factors for prostate cancer. *Br J Cancer* 1996;74:1682-1686.
19. Hsing AW, Chua S, Gao YT, et al. Prostate cancer risk and serum levels of insulin and leptin. *J Natl Cancer Inst* 2001;93:783-789.
20. Lavecchia C, Negri E, Franceschi S, Davanzo B, Boyle P. A case-control study of diabetes mellitus and cancer risk. *Br J Cancer* 1994;70:950-953.